U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Bayesian Design and Analysis (Clinical Regulatory Perspective)

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Outline

- OCTGT
- Applications: Past Experience/Potential Applications
- Clinical Interpretation Challenges
- Summary

Organization

- CBER (Center for Biologics Evaluation and Research): vaccines, blood and blood products, human tissue/tissue products for transplantation, cells, gene therapy
  - Office of Cellular, Tissue, and Gene Therapy
  - Office of Vaccines Research and Review
  - Office of Blood Research and Review
- CDER (Center for Drug Evaluation and Research): drugs, some biologicals
- CDRH (Center for Devices and Radiological Health): devices for treatment, implants, diagnostic devices
- CVM
- CFSAN
- NCTR

OCTGT Regulation

- Cellular therapies
- Tumor vaccines
- Gene therapies
- Tissue and tissue based products
- Xenotransplantation products
- Combination products
- Devices used for cells/tissues
- Anti-idiotype antibodies

Applications: Experience

- Confirmatory trial
- Predictive probability of success

Confirmatory Trial: P000036

- Indication:…indicated for use for the treatment of full-thickness diabetic foot ulcers greater than six weeks duration which extend through the dermis, but without tendon, muscle, joint capsule or bone exposure…
- Description:…cryopreserved human fibroblast-derived dermal substitute; it is composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold
- www.fda.gov/cdrh/pdf/p000036b.pdf

P000036 cont'd

- Study design:
  - Randomized study (experimental treatment plus standard care versus standard care)
  - Primary effectiveness: complete wound closure by week 12
  - Frequentist analysis plan
- Interim analysis: Relative benefit in patients with ulcer duration > 6 weeks at entry
- Confirmatory study using Bayesian design to incorporate prior information

Predictive Probability of Success: P970015

- Indication:…spinal fusion procedures in skeletally mature patients with degenerative disc at one level from L2-S1
- Description: …hollow threaded cylinder with a removable endcap…manufactured from titanium alloy
- www.fda.gov/cdrh/pdf/970015b.pdf

970015 cont'd

- Study design:
  - Initially designed as randomized non-inferiority study
  - Non-randomized treatment group later added
- Data analysis: at time of data analysis, not all patients had reached 2 year timepoint for safety and effectiveness assessment
- Analysis of predictive probability of non-inferiority at the end of the trial noted > .95 success even for non-inferiority margin of .04

Potential Applications

- Selecting a treatment regimen
- Comparability testing
- Small populations/limited product availability/relevant available information/convergent understanding
- Pooling centers
- Borrowing strength for controls

Clinical Interpretation Challenges

- Planning the trial:
  - Prior information
  - Design elements including mathematical model
  - Decision criteria
- Type I error
- Communication of results

Planning the Trial: Prior Information

- Prior information can consist of:
  - Clinical trials with same or similar product
  - Registries or case series
  - Pilot studies
- Questions:
  - How were the prior sources of information selected?
  - How similar is the product?
  - How complete is the information from each source?
  - Patient level data?

Prior Information, cont'd

- How similar are the protocols to the proposed study in terms of:
  - Patient management
  - Endpoints
  - Study duration
- How similar are the patient populations?
- Physician training and experience?
- Time period of the study?
- Etc.

Planning the Trial: Study Design Elements

- Familiar issues from frequentist trials are important here as well:
  - Endpoint selection
  - Choice of control
  - Covariates
  - Minimum size for safety as well as effectiveness
  - Etc.
- All of these items need a clinical assessment

Planning the Trial: Study Design Elements

- Assumptions in Bayesian model have clinical interpretation as well:
  - Exchangeability of patients
  - Exchangeability of studies
  - Prediction of later follow-up data from earlier information
- Important to explain the assumptions and their clinical basis

Planning the Trial: Decision Criteria

- P(proportion of successIdata): based on updated data combined as per model
- Credible interval:
  - Around what parameter?
  - What interval is good enough?
- Acceptable credible interval needs clinical interpretation

Type I Error Control

- Trial simulation
- Parameters are fixed at borderline values for which product should not be approved
- Proportion of successful trials gives estimate of type I error rate
- Choice of parameter value needs clinical interpretation

Communication of results: Labeling strategies

- Provide parameter estimate
- Provide tables with raw data
- Provide frequentist and Bayesian analysis side by side

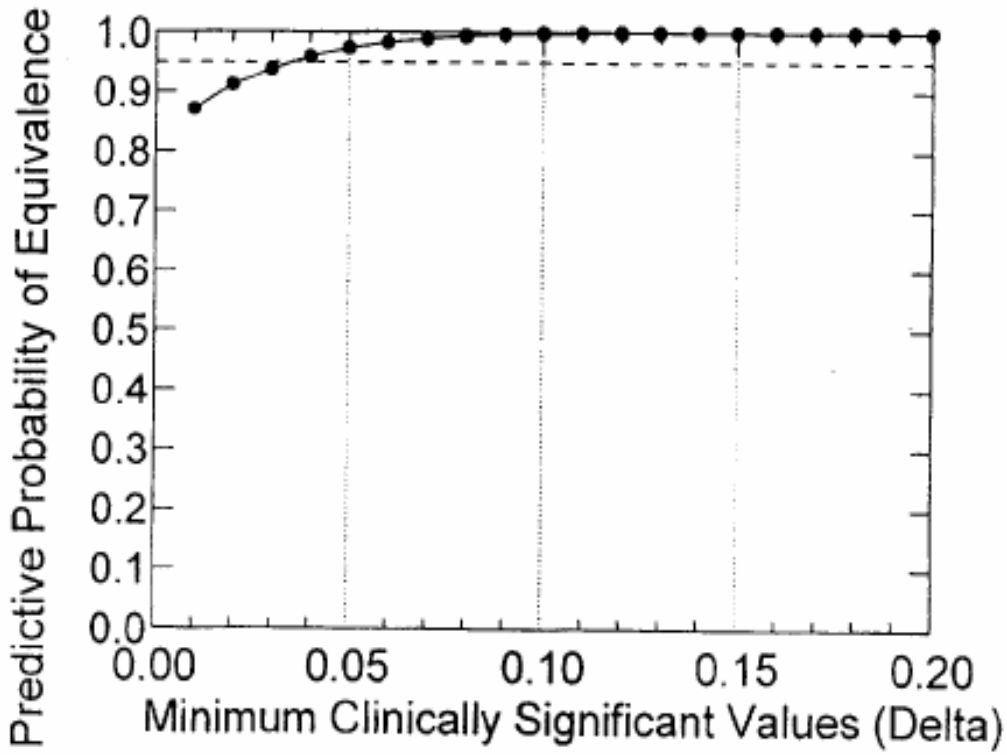
Table XV-Intent-to Treat Analysis for INTER FIX ™ Device
Deaths, Secondary Surgery Failures, Lost-to Follow, and Missing Observations Are Considered as Failures and Are Included in the Denominator of the Rates

	12 Month Rates Randomized	12 Month Rates Randomized and Nonrandomized	24 Month Rates Randomized
Fusion	75.3% (58/77)	67.3% (107/159)	85.1% (63/74)
Oswestry Pain/ Disability Improvement Patients with at least 15 Point Improvement from Pre-Op	44.2% (34/77)	42.1% (67/159)	54.1% (40/74)
Neurological Status Maintenance or Improvement	85.7% (66/77)	78.6% (125/159)	85.1% (63/74)
Overall Success	36.4% (28/77)	34.0% (54/159)	50.0% (37/74)
Secondary Surgery Failures			
Nonunions [3]	2	2	2
Other [4]	1	8 [5]	3
Deaths	0	0	0

[3] These Patients are included in the fusion rate calculation but are otherwise considered as failures for clinical trial purposes.
[4] Patients due for follow up at that period who had secondary surgeries for reasons other that nonunion are considered failures for clinical trial purposes.
[5] Includes 3 patients who did not receive study treatments due to surgical events.

Figure 1

Bayesian Predictive Probabilities of Equivalence*
For Overall Success - Includes Second Surgery Failures



*INTER FIX™ Device No Worse Than Control

Note: Overall success rates were based on patients with available data and did not include deaths, loss-to-follow-ups, or missing observations.

Summary

- Bayesian design and analysis has been used in a number of regulatory submissions
- Collaboration between clinicians and statisticians is critical:
  - Clinical interpretation of study design is important
  - Clinical interpretation of decision criteria is important
  - Addressing both in a submission for a clinical study will be a key element of success

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